A6-03 **Cancer Genetics and Tumor Biology, Mon, 13:45 - 15:30**

A possible role for the intracellular Ca2+-homeostasis in the development of cisplatin-resistance in squamous lung carcinoma cells

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Background: In the treatment of lung cancer, the effectiveness of chemotherapy is hampered by the development of therapy-resistance. Calcium is a universal second messenger involved in the regulation of virtually all cell function including apoptosis and cell death. Aim of this study was to investigate if the intracellular Ca2+-homeostasis of lung cancer cells may influence the development of therapy-resistance to cisplatin.

Methods: ATP served as an agonist to stimulate squamous lung carcinoma cells (EPLC) and the increase in cytoplasmatic calcium ([Ca2+]c) was quantified using fluorescence microscopy. The Ca2+-indicator rhod-2 was used to quantify the mitochondrial Ca2+-content. EPLC cells were exposed to 0.5, 1 and 2 μg/ml cisplatin for 3h simulating the in vivo pharmacokinetics. The Ca2+-chelator BAPTA was used to study the effects of a reduced [Ca2+]c on the effectiveness of cisplatin.

Results: Using appropriate inhibitors, we could show that the ATP-induced Ca2+-increase was due to Ca2+-release from the sarcoplasmic reticulum involving IP3- and Ryanodine-receptors with Ca2+-influx from the extracellular space playing a minor role. Exposure to cisplatin led to a time dependent increase in the mitochondrial Ca2+-content. After 4 "cycles" of cisplatin the EPLC cells showed an increased survival compared to naïve EPLC cells. This therapy-resistance could be mimicked buffering [Ca2+]c with BAPTA. In the resistant clone, the ATP-induced Ca2+-increase was found to be significantly reduced compared to naïve cells.

Conclusions: The intracellular Ca2+-homeostasis of lung carcinoma cells plays a significant role in the development of cisplatin-resistance and may therefore constitute a novel approach to overcome therapy-resistance.

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A6-04 **Cancer Genetics and Tumor Biology, Mon, 13:45 - 15:30**

Expression of vascular endothelial growth factors (VEGFs) A, C, D and receptors (VEGFRs) 1, 2 and 3, in both tumor cells and tumor stroma of non-small cell lung cancer (NSCLC): correlation with lymph node metastasis

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Purpose: Nodal status is an important prognostic factor and a major determinant for the staging and clinical management of NSCLC. The vascular endothelial growth factors (VEGFs) and the vascular endothelial growth factor receptors (VEGFRs) are important molecular markers in angiogenesis and lymphangiogenesis. In this study, we aimed to extensively investigate the correlations between lymph node metastasis and the VEGFs and VEGFRs in tumor cells as well as in the tumor stroma.

Methods: Tumor tissue samples from 335 resected patients with stage I to IIIA were obtained and tissue microarrays were constructed from duplicate cores of tumor cells and surrounding stromal tissue from each resected specimen. Immunohistochemistry was used to evaluate the expression of VEGF-A, VEGF-C, VEGF-D, VEGFR-1, VEGFR-2 and VEGFR-3.

Results: There were 232 lymph node metastasis negative- and 103 lymph node metastasis positive patients (76 N1, 27 N2). In univariate analyses (Chi-square test), high tumor cell expression of VEGF-A (P = .011) and VEGFR-3 (P < .001) correlated with lymph node metastasis. In tumor stroma, however, low expression of VEGF-A (P = .037) and VEGFR-3 (P = .033), correlated with lymph node metastasis. There were no significant correlations between tumor cell or stromal expression of VEGF-C, VEGF-D, VEGFR-1 or VEGFR-2 and lymph node metastasis. Though, high tumor cell expression of VEGFR-1 (P = .065) and low stromal expression of VEGFR-1 (P = .075) tended towards correlation with lymph node metastasis. In multivariate analyses (Binary logistic regression), including clinicopathogical variables and angiogenic markers, high tumor cell expression of VEGF-A (P = .032, HR 1.8, 95% CI 1.1-3.1), low stromal expression of VEGF-A (P = .025, HR 3.1, 95% CI 1.2 - 8.3) and poor differentiation (P < .001, HR 3.4, 95% CI 2.0-5.9) correlated with lymph node positive patients. High tumor cell expression of VEGFR-3 (P < .001, HR 6.1, 95% CI 2.1-17.6) and vascular infiltration (P = .011, HR 3.9, 95% CI 1.4-11.2) correlated with N2 positivity.

Conclusion: In tumor cells, there are strong correlations between high VEGFR-3 expression and N2-status and high VEGF-A expression and lymph node metastasis. While in stroma, low VEGF-A expression is associated with lymph node metastasis.

A6-05 **Cancer Genetics and Tumor Biology, Mon, 13:45 - 15:30**

Clinicopathologic Implications of minimal genomic alteration regions (MAR) identified in non-small cell lung cancer by using whole genome array-CGH

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Background: Lung cancer is the most common incident form of malignancy and also the leading cause of cancer death worldwide. Although many genomic alterations have been observed in lung cancer, their clinicopathological significance has not been thoroughly investigated. This study screened the genomic aberrations across the whole genome of non-small cell lung cancer cells with high-resolution and investigated their clinicopathological implications.

Method: One Mb-resolution array comparative genomic hybridization (array-CGH) was applied to 31 squamous cell carcinomas and 24 adenocarcinomas of lung. Copy number alteration was detected by using web based array-CGH analysis software named arrayCyGHt (http://genomics.catholic.ac.kr/arrayCGH/). The recurrent genomic alterations were analyzed for the association with the clinicopathological features of lung cancer. Significance of the association between MAR and